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Extended Summaries SCI Pesticides Group and RSC Biological and Medicinal Chemistry Group Symposium: Advances in the Chemistry of Crop Protection

The following are extended summaries based on papers presented at the meeting 'Advances in the Chemistry of Crop Protection' organised by P. J. Crowley, G. Mitchell, G. Keen, J. Pickett and P. D. Riordan on behalf of the SCI Pesticides Group and the RSC Biological and Medicinal Chemistry Group and held on 9–11 September 1996 at Churchill College, Cambridge. The contents are entirely the responsibility of the authors and do not necessarily reflect the views of the Editorial Board of Pesticide Science.

Synthesis and Insecticidal Activity of Heterocyclic Substituted Dihydropyrazoles

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At the beginning of the 1970s, the 3-phenylpyrazoline-1-carboxanilides, such as PH 60-41, were discovered as a new, highly active class of insecticide.[1] In contrast to the benzoylureas such as diflubenzuron, these compounds are not inhibitors of chitin biosynthesis. These new, highly active compounds act on the nervous system by a novel but as yet unknown mechanism.[2,3] During the course of further work in this class an additional phenyl ring was introduced into the 5-position of the pyrazoline, and this led to a further increase in activity.[4] Moving this phenyl ring from the 5- to the 4-position gave PH 60-42[5] with very good insecticidal activity against a broad spectrum of pests, and subsequent work focused mainly on the 3,4-diphenylpyrazolines.[6,7]

The extremely high potential activity coupled with a novel mechanism of action also encouraged us to initiate synthetic work in this class. A thorough review of the literature led us to believe that the 4-position offered the greatest potential for variation. Alkyl, aminoethyl and cyanoethyl groups had all been shown to be tolerated in the position.[8–10] In 1987, pyrazolines were reported with a 4,4-disubstitution in which the phenyl ring was no longer present.[11] RH 3421, in which the 4-position bears a methyl and a carbomethoxy group, was presented as the best derivative.[12] Relatively little was known about heterocyclic substituted pyrazolines. In 1973, pyrazolines substituted in the 5-position by thiophene, pyridine, furan and pyrrole were reported[13] and in 1976 pyrazolines substituted in the 3-position by thiophene.[8] This patent application also claimed pyrazolines substituted in the 4-position by pyridine and thiophene but did not provide any examples.

As heterocycles had hardly been described in the 4-position and up to that point no substitution had been reported in which the substituent was bonded via a hetero-atom to the C-4 atom of the pyrazoline, we decided to start with the synthesis of azole derivatives of pyrazoline bonded via nitrogen to this position. The synthesis of these pyrazolines was carried out by analogy with that of the compounds already reported.[8,13] The azole-substituted acetophenones required, such as the triazole shown in Fig. 1, are easily made from ω-bromoacetophenones and the corresponding azole. Mannich condensation with aqueous formaldehyde (**A**, Fig. 1) provided the unsaturated ketone, which reacted smoothly with hydrazine to give the pyrazoline. Reaction with 4-trifluoromethoxyphenylisocyanate gave **1**, which showed very good activity in our tests at 1 mg litre^{-1} against Plutella and Spodoptera spp. We were able to make a series of azole-substituted pyrazolines by this reaction sequence. An alternative synthesis by reacting the azolyl-acetophenone with *N*,*N*-

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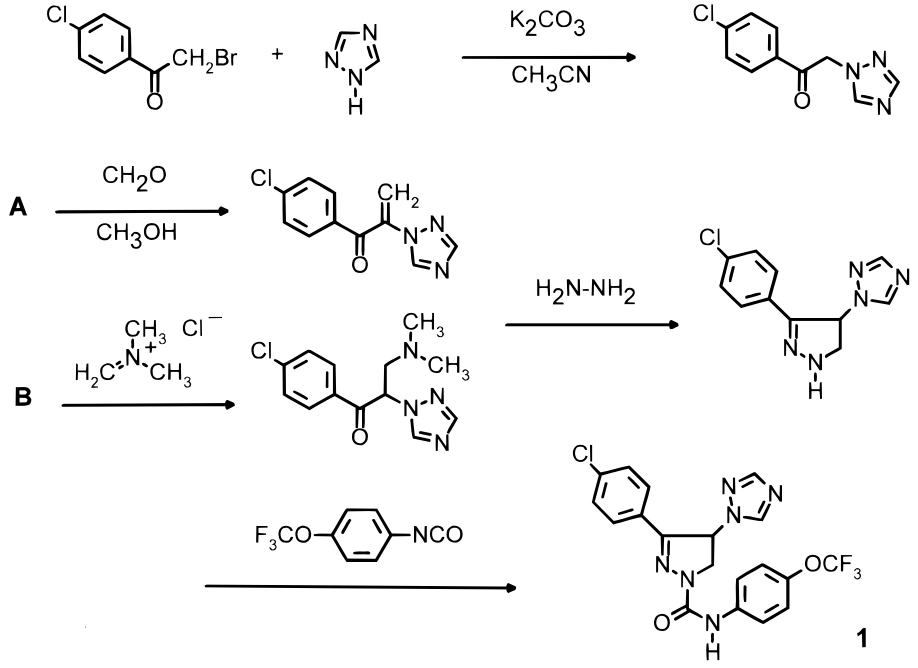
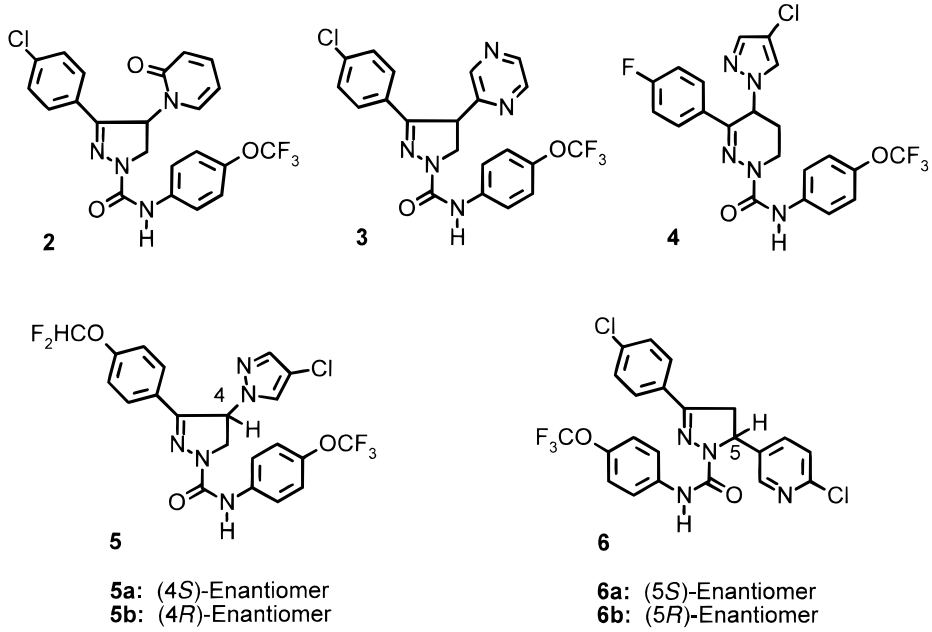


Fig. 1. Synthesis of 4-triazolylpyrazoline-1-carboxanilide.

dimethylmethyleneammonium chloride (**B**, Fig. 1) gave the Mannich base, which was immediately reacted with hydrazine hydrate to yield the pyrazoline.

The corresponding pyrazolines substituted with 6-ring nitrogen heterocycles connected via the nitrogen, such as pyridin-2-one **2** (Fig. 2), were easily made by the analogous route to the azole derivatives, through reaction of 2-hydroxypyridine with bromoacetophenone, for example. The heterocyclic-substituted pyrazolines connected via carbon were made by alternative routes. Thus metallation of 2-methylpyrazine in THF with *n*-butyl-lithium and reaction with methyl 4-chlorobenzoate gave the pyrazine-substituted acetophenone, which yielded the Mannich adduct with *N*,*N*-dimethylmethyleneammonium chloride. Reaction with hydrazine hydrate gave the pyrazoline substituted in the 4-position by pyrazine in good yield. The carboxanilide **3** (Fig. 2) was obtained by reaction with 4-trifluoromethoxyphenylisocyanate and shows excellent insecticidal activity.

Tetrahydropyridazine-carboxanilides are formally regarded as derivatives of pyrazolines in which the 5-membered ring has been expanded by an additional methylene group. The following route was used for the synthesis. The required 4-chlorobutyrophenones were obtained in good yield by Friedel-Crafts reaction with



5a: (4*S*)-Enantiomer
5b: (4*R*)-Enantiomer

6a: (5*S*)-Enantiomer
6b: (5*R*)-Enantiomer

Fig. 2. Structures of compounds referred to in the text.

4-chlorobutyroyl chloride. These could be brominated easily in the 2-position and then reacted with 4-chloropyrazole in the presence of potassium carbonate, to give the desired 2-pyrazolyl-4-chlorobutyrophenones. These reacted with excess hydrazine hydrate to give the hydrazones, which ring-closed during the reaction with arylisocyanates to form the final products, for example, **4** (Fig. 2). Expanding the pyrazoline ring by inserting a methylene group led to a fall in insecticidal activity.

The heterocyclic pyrazolines were highly effective against beetle larvae and caterpillars. In most species (e.g. *Phaedon cochleariae* F., *Plutella xylostella*, L., Spodoptera and Heliothis spp.) full insecticidal activity in laboratory dip tests was found as low as 8 or 1.6 mg litre^{-1}. The onset of action was somewhat slower than that of pyrethroids or organophosphates but faster than that of IGRs. They have not been found to be cross-resistant to any established class of insecticide on the market.

The structure–activity relationships of 5- and 6-ring heterocycles are outlined in Fig. 3. The best activity resided with the azoles substituted by halogen, bromo- and chloropyrazole being best of all. The 5-chloro-2-pyridyl residue was on the same level as chloropyrazole. 1,2,4-Triazole and pyrazine also had very good activity. The *N*-substituted 2-pyridone was surprisingly good, but pyrimidones were much less active, as was iodopyrazole. Unsubstituted pyrazole, imidazole and pyrimidine were markedly less active, and alkyl substitution was unfavourable.

The structure–activity relationships for the aryl substituents were elucidated. The phenyl ring in the 3-position on the central pyrazoline ring could tolerate a large number of different substituents, although the 4-position was favoured. 3- and 3,4-substitution also led to active compounds. Even with unsubstituted phenyl it was possible to get reasonably active compounds. The best substituents were found to be 4-$OCHF_2$, Br and Cl. In contrast to the phenyl in the 3-position, the phenyl ring of the carboxanilide group was much more sensitive to variation of substitution. Electron-donating substituents such as alkyl or alkoxy groups drastically reduced activity. The unsubstituted phenyl ring was almost inactive. The best activity was shown by 4- and 3,4-substitution; 2-substitution led to loss of activity. The best substituents were electron-withdrawing—4-OCF_3, CF_3, Br or Cl. An additional F or Cl in the 3-position could be tolerated. However, ringing the changes on all three variables might lead to new constellations of substituent combinations with good insecticidal activity.

Apart from the substitution in the 4-position of the pyrazolines, we were also interested in heterocyclic substitution in the 5-position. Pyrazolines substituted in this position by 2-pyridyl, 3-pyridyl and 4-pyridyl had already been described.[13] Reaction of 4-chloroacetophenone with 2-chloro-5-pyridinealdehyde in the presence of potassium hydroxide as base afforded the unsaturated ketone, which reacted smoothly to give the pyrazoline with hydrazine hydrate. The carboxanilide **6** (Fig. 2) showed very good activity against caterpillars.

It had been reported that among the 3,4-aryl-substituted pyrazolines only the (4*S*)-enantiomer is responsible for the insecticidal activity.[14] The enantiomers had been separated via derivatisation to diastereomers. It was therefore particularly interesting to find out whether activity in the series of pyrazolines substituted by azoles in the 4-position is due to a single isomer. As

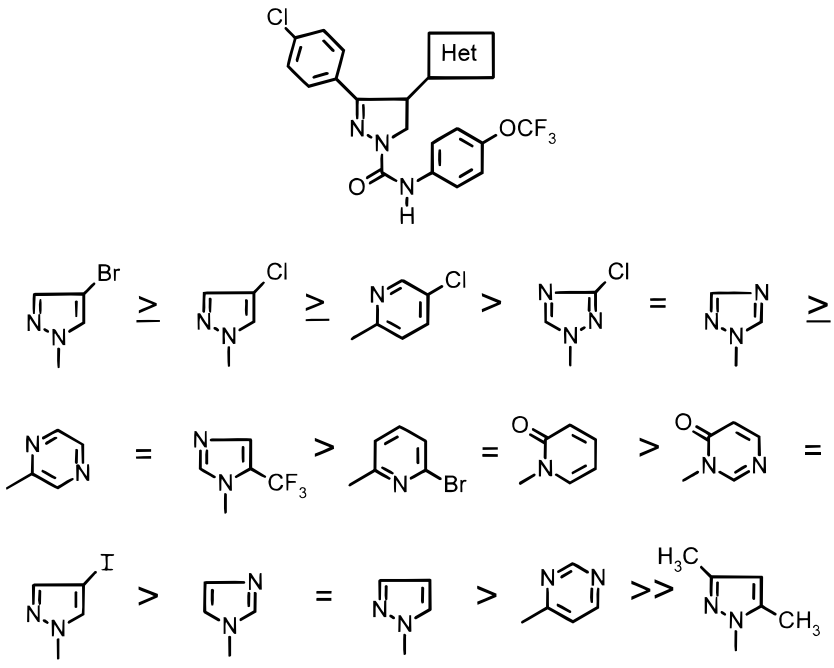


Fig. 3. Structure–activity relationship for heterocycles.

a direct separation of the enantiomers of pyrazolines substituted in the 5-position had not been reported, and as it was also of interest for structure–activity relationships, we separated **6** into its enantiomers. The chromatographic separation of the racemic products **5** and **6** could be achieved with extremely high enantioselectivity on chiral stationary polyamide phases.[15]

X-ray crystal structure analysis was carried out on the separated enantiomers **5a**, **5b** and **6a**, **6b**, and their biological activities studied. The (4*S*)-chloropyrazole enantiomer **5a** contained all the activity, and showed excellent effect in our tests against Spodoptera spp. and Heliothis spp. at 0·32 mg litre^{-1}. The (4*R*)-chloropyrazole enantiomer **5b** was practically inactive. In the case of the pyrazoline substituted in the 5-position by chloropyridine (**6**, Fig. 2), the (5*S*)-enantiomer **6a** was also the sole bearer of the insecticidal activity. When the active (4*S*)-chloropyrazole enantiomer **5a** and the active (5*S*)-chloropyridine enantiomer **6a** were overlaid, it was found that the substituents in the 4- and the 5-positions occupied almost the same space. If the inactive (5*R*)-chloropyridine enantiomer **6b** was laid on top of the active (4*S*)-chloropyrazole enantiomer **5a**, it was found that, in the inactive enantiomer **6b**, the pyridine residue projected into a space on the opposite side of the plane occupied by the (4*S*)-chloropyrazole, and this presumably explains its inactivity.

To summarise, X-ray structural analysis has shown that the same space-filling characteristics are required for insecticidal activity in the 4-substituted and the 5-substituted pyrazolines.

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